AWARD NUMBER: W81XWH-15-1-0670

TITLE: CDK5-A Novel Role in Prostate Cancer Immunotherapy

PRINCIPAL INVESTIGATOR: Dr. Barry Nelkin

CONTRACTING ORGANIZATION: Johns Hopkins University
Baltimore, MD 21287

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Johns Hopkins University
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our project will establish the role of CDK5 in promoting the immunosuppressive microenvironment in prostate cancer, and identify optimal strategies for incorporation of CDK5 inhibition to augment the efficacy of immunotherapy for prostate cancer. We will confirm our observation of the involvement of a T cell antitumor response in impaired growth of prostate cancer in immunocompetent murine models of prostate cancer, and characterize the changes induced in immune cells in the tumors. Preclinical translational studies, employing a CDK5 inhibitor in combination with immunotherapies, including immune checkpoint blockers, a prostate cancer vaccine, and other agents will be conducted and optimized in vivo in an immunocompetent prostate cancer model. If successful, these therapeutic strategies can be rapidly advanced to clinical evaluation. In this reporting period, our most significant finding was that *Cdk5* gene silencing by shRNA in the TRAMP-C2 prostate cancer cell line sensitized allografts to combined immune checkpoint blockade, using anti-CTLA4 and anti-PD-1 antibodies. The significance of this finding is that it provides a promising potential therapeutic strategy for prostate cancer, using a combination of CDK5 inhibition and immune checkpoint blockade.

15. SUBJECT TERMS
None listed

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1. **INTRODUCTION:** Our project will establish the role of CDK5 in promoting the immunosuppressive microenvironment in prostate cancer, and identify optimal strategies for incorporation of CDK5 inhibition to augment the efficacy of immunotherapy for prostate cancer. If successful, these therapeutic strategies can be rapidly advanced to clinical evaluation. Thus, in Specific Aim 1, we will explore mechanisms of immune system activation by Cdk5 deletion in prostate cancer. We will confirm the involvement of a T cell antitumor response in impaired growth of prostate cancer in the TRAMP Cdk5$^{-/-}$ model, by ablating T cells therein. We will then characterize the changes induced in immune cells in the tumors, using FACS and IHC, and in cytokines, using a protein microarray. Functional assays of T cell activation, including proliferation and CTL assays, will be performed. These findings will be extended to other prostate cancer models. In Specific Aim 2, preclinical translational studies, employing a CDK5 inhibitor in combination with immunotherapies, including immune checkpoint blockers, a prostate cancer vaccine, and other agents based on our findings in Specific Aim 1, will be conducted and optimized in vivo in an immunocompetent prostate cancer model, for potential rapid translation to clinical evaluation.

2. **KEYWORDS:** Prostate cancer, CDK5, immunotherapy, vaccine, tumor microenvironment

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

Major Task 1: Involvement of T cell anticancer immune response in impaired growth of TRAMP *Cdk5*$^{-/-}$ model. Months 1-10. Completed, month 10.

Major Task 2: Characterization of antitumor immune response in TRAMP *Cdk5*$^{-/-}$ tumors. Months 1-14. Completed, month 16.

Major Task 3: Validation of findings in other prostate cancer models. Months 12-24. 20% complete.

Major Task 4: Studies on prostate cancer with ablated *Cdk5*. TRAMP-C2 cells with and without *Cdk5* knockdown will be implanted orthotopically in syngeneic mice, and treated with selected immunotherapies. Mice will be monitored for tumor growth and survival. Months 16-30. Completed, month 24.

Major Task 5: Studies on prostate cancer treated with a pharmacological Cdk inhibitor. TRAMP mice will be treated with a combination of a CDK5 inhibitor and best immunotherapy (from Specific Aim 2, Major Task 4). Mice will be monitored for tumor growth and survival. Dosing sequences will be compared. Months 20-30. Not yet initiated.

Major Task 6: Data will be analyzed, and potential clinical development will be discussed and planned with pharmaceutical company collaborators and liaisons. Months 24-30 and beyond. 10% complete

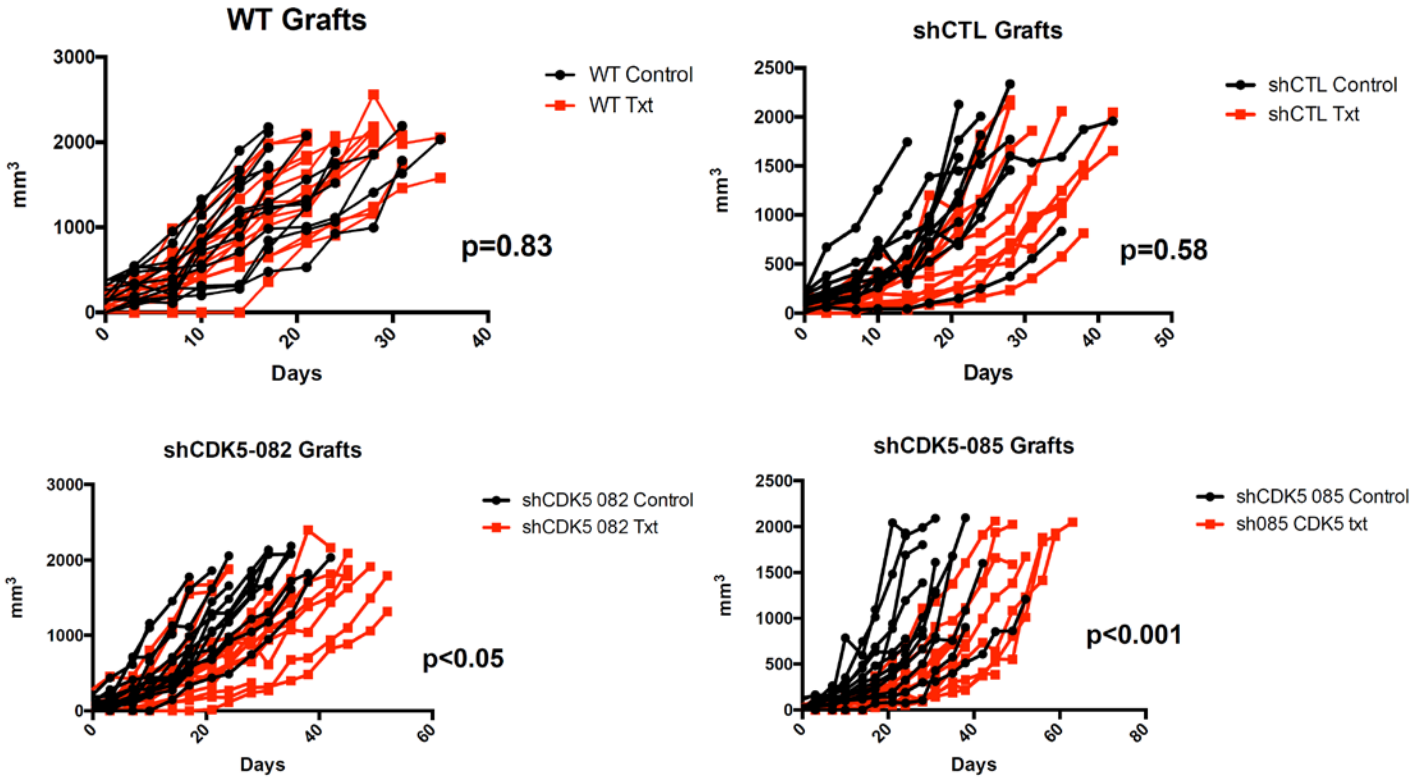
What was accomplished under these goals?

Major activities and specific objectives.

We concentrated on Major Tasks 2 and 4, characterization of the role of Cdk5 in the antitumor immune response in the TRAMP murine model of prostate cancer and immunotherapy in the TRAMP model with *Cdk5* knockdown.

Significant results.

Stable populations of TRAMP-C2 with shRNA *Cdk5* knockdown were established by lentiviral transduction using two different *Cdk5* targeting clones and a non-targeting control. Bilateral flank xenografts (WT, shCTL, shCDK5-082, shCDK5-085) were established in C57BL/6Tac mice (N=15 per cell line). When tumors were first palpable, mice with tumors from each cell line were randomized into two treatment groups and treated with either a mixture of anti-CTLA-4 (9D9) and anti-PD-1 (RMP1-14) antibodies or isotype control by IP injection (200 ug each antibody, weekly x 3 doses, N=7-8 per group). We combined CTLA-4 with PD-1 because of previous reports that showed no single agent efficacy (Yu et al, PNAS 109:6187-6192, 2012). Twice weekly measurements of allograft size were conducted until the tumors reached maximum permitted size. Volume calculated as $(LxW^2)/2$. Comparisons between treatment groups were calculated using Rate Based *T/C* (Hather et al, Cancer Inform. 13Suppl 4:65-72, 2014) because this method provides equal power compared to traditional methods using fewer animals, and can be applied to non-synchronous allograft lines, such as TRAMP-C2. Overall growth showed no difference between WT, shCTL, and shCDK5 lines, in contrast to the autochthonous tumors. Combination anti-CTLA-4 and anti-PD-1 had no significant effect on WT or shCTL tumors, but significantly decreased the growth rate of both shCDK5 knockdown cell lines ($p<0.05$ for shCDK5-082, $p<0.001$ for shCDK5-085).



What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

Our major focus in the next reporting period will be on the experiments outlined in Major Tasks 3, 5 and 6: 1) confirmation of our findings in a second mouse prostate cancer model (in this case, in the Myc-CaP cell line, with *Cdk5* knockdown using shRNA), 2) the effect of a combination of a pharmacological CDK5 inhibitor and

immune checkpoint therapy. We will likely use CYC065 as the CDK inhibitor, since it is in active clinical development, thus facilitating subsequent translation and 3) analyzing our data, preparation and submission of a manuscript, and discussion with pharmaceutical companies the potential translation of our findings for clinical development.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

The finding, described above, that CDK5 has a role in T cell based antitumor response in prostate cancer is likely to establish CDK5 as a promising immunotherapeutic target in prostate cancer. The impact awaits our wider dissemination of this finding as a manuscript.

Our finding that CDK5 ablation in TRAMP-C2 sensitizes their allografts to combined immune checkpoint blockade provides a promising potential therapeutic strategy for prostate cancer; development of this avenue will be pursued further in the remainder of this project as well as in subsequent studies.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

As discussed last year, for Major Tasks 5 and 6, we have been planning to use either dinaciclib (Merck) or roniciclib (Bayer), multi-CDK inhibitors which were in mid to late stage clinical development. We have active MTAs for both compounds. Unfortunately, both Merck and Bayer have terminated clinical development of these compounds. The compounds are still well suited, as “tool compounds,” for the preclinical studies in Major Task 5. We were discussing with other pharmaceutical companies the potential use of their CDK inhibitors in clinical development. We have this week completed an MTA with Cyclacel Pharmaceuticals for use of their CDK inhibitor, CYC065, currently in Phase 1 clinical development. In addition, we have entered into a formal collaboration with a large pharmaceutical company, for screening their multimillion compound drug library to identify specific CDK5 inhibitors.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

6. PRODUCTS:

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers, and presentations.

Nothing to Report

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Barry Nelkin, Ph.D.*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Nelkin co-directs all aspects of this project*
Funding Support:	

Name:	*Charles Drake, M.D., Ph.D.*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Drake co-directs all aspects of this project*
Funding Support:	

Name:	*Brian Simons, D.V.M., Ph.D.*
Project Role:	*Research Associate*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*3*
Contribution to Project:	*Dr. Simons performs and interprets the in vitro and in vivo experiments, and participates in supervising the Research Specialist, Ms. Ybanez*
Funding Support:	*Department of Urology startup funds*

Name:	*Maria Ybanez*
Project Role:	*Research Specialist*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*7*
Contribution to Project:	*With Dr. Simons, Ms. Ybanez performs the in vitro and in vivo experiments*
Funding Support:	

Name:	*Rebecca Miller*
Project Role:	*Research Specialist*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*2*
Contribution to Project:	*Ms. Miller has taken over Ms. Ybanez's duties. With Dr. Simons, Ms. Miller performs the in vitro and in vivo experiments*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes, see next pages for Drs. Nelkin and Drake's Other Support

What other organizations were involved as partners?

- **Organization Name:** Columbia University Medical School
- **Location of Organization:** New York, NY
- **Partner's contribution to the project**

  As discussed above, co-PI Dr. Charles Drake has now moved to Columbia University.

OTHER SUPPORT

NELKIN, BARRY D.

ACTIVE

W81XWH-15-1-0670 (PI: Nelkin/Drake)
Title: CDK5-A Novel Role in Prostate Cancer Immunotherapy
Time commitment: 1.92 calendar
Supporting agency: CDMRP
Procuring Contracting/Grants Officer: Kathy Robinson
Address of Grants Officer: 820 Chandler Street, Fort Detrick, MD
Performance period: 09/30/2015-09/29/2018
Level of funding:
Project's Goal(s): The goal of this project is to develop a novel, effective targeted therapeutic strategy for advanced prostate cancer, blocking several of the most common resistance mechanisms to androgen deprivation therapy (ADT), that underlie progression to castration resistant prostate cancer (CRPC)
Specific Aims: 1. Effect of dinaciclib on androgen receptor (AR) S81 phosphorylation and function. **2**. Effect of dinaciclib, alone and in combination with inhibitors of potential compensatory signaling pathways, in human prostate cancer cell lines and xenografts. **3**. Effect of dinaciclib combinations in a model of prostate cancer bone metastasis.
Project Overlap or Parallel: No scientific or budgetary overlap.

AWARDED SINCE LAST SUBMISSION
None

COMPLETED SINCE LAST SUBMISSION

SCH727965 (PI: Azad)
Title: LOI 9231: A Phase I Trial of Dinaciclib (SCH727965) and MK2206 in Advanced Solid Tumors with an Expansion Cohort in Advanced Pancreatic Cancer
Time commitment: 0.30 calendar
Supporting agency: Lustgarten Foundation
Procuring Contracting/Grants Officer: Mila McCurrach
Address of Grants Officer: 1111 Stewart Ave, Bethpage, NY 11714
Performance period: 05/01/2013-04/30/2017
Level of funding:
Project's Goal(s): The main project goals are to exhibit that the combination inhibition of downstream effectors of the Ras pathway with MK-2206 and dinaciclib will be tolerable and effective in advanced pancreatic cancer.
Specific Aims: 1. Determine the maximum tolerated dose (MTD), safety, and toxicity of the combination of MK-2206 and dinaciclib in patients with advanced pancreatic adenocarcinoma. **2**. Assess the preliminary efficacy of the combination of MK-2206 and dinaciclib in metastatic pancreatic cancer patients as determined by disease control rate in an expansion cohort of patients at the MTD. **3**. Characterize the pharmacokinetic (PK) profile of the combination of MK-2206 and dinaciclib. **4**. Analyze pre-treatment tumor specimens for activation of RAS downstream pathway signaling as potential predictors of treatment benefit. **5**. Correlate post-treatment pharmacodynamic (PD) changes in tumor biopsies and peripheral blood mononuclear cells with MK-2206 and dinaciclib treatment to demonstrate proof-of-concept and assess for post-treatment predictive biomarkers.
Project Overlap or Parallel: No scientific or budgetary overlap.

OTHER SUPPORT

DRAKE, Charles G.

ACTIVE:

90061946 (Drake)
Title: Epigenetic Drugs and Immuno Therapy for Prostate Cancer (EDIT-PC)
Effort: 1.2 calendar months (10% effort)
Supporting Agency: Prostate Cancer Foundation
Name of Procuring Contracting/Grants Officer: Howard R. Soule, PhD
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401
Performance Period: 12/24/2014-12/23/2017
Level of Funding:
Project's Goal: To evaluate the ability of a novel, multivalent cancer vaccine based on attenuated listeria monocytohenes (*Lm)* to induce prostate cancer-specific immune responses, and to attenuate tumor progression
Specific Aims: 1.) Evaluate a novel, trivalent prostate cancer vaccine based on an attenuated listeria platform for safety, tolerability and preliminary evidence of efficacy in men with metastatic castration-resistant prostate cancer (mCRPC). 2.) Determine the magnitude and breadth of antigen-specific T and B cell immune responses induced by this novel vaccine. 3.) Using biopsies of metastatic lesions, quantify the induction of a pro-inflammatory immune infiltrate as well as expression of checkpoint ligands (including PD-L1) for potential utility as predictors of response and/or resistance.
Role: PI
Overlap: None

W81XWH-15-1-0670 (Nelkin/Drake)
Title: CDK5-A Novel Role in Prostate Cancer Immunotherapy
Effort: 0.48 calendar months (4% effort)
Supporting Agency: CDMRP
Name of Procuring Contracting/Grants Officer: Kathy Robinson
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD
Performance Period: 10/01/16-09/29/2018
Level of Funding:
Project's Goal: The goal of this project is to develop a novel, effective targeted therapeutic strategy for advanced prostate cancer, blocking several of the most common resistance mechanisms to androgen deprivation therapy (ADT), that underlie progression to castration resistant prostate cancer (CRPC)
Specific Aims: 1) Effect of dinaciclib on androgen receptor (AR) S81 phosphorylation and function. 2) Effect of dinaciclib, alone and in combination with inhibitors of potential compensatory signaling pathways, in human prostate cancer cell lines and xenografts. 3) Effect of dinaciclib combinations in a model of prostate cancer bone metastasis.
Role: MPI
Overlap: None

P30CA006973 (PI: Nelson/Drake)
Title: Regional Oncology Research Center (Flow Cytometry/Human Immunology Shared Resources) Time **Commitment:** 1.32 calendar
Supporting Agency: National Cancer Institute
Procuring Contracting/Grants Officer: Michael Zarkin
Address of Funding Agency: 6120 Executive Blvd, Suite 243 Rockville, MD 20892
Performance Period: 05/07/1997-04/30/2017
Level of Funding:

Project's Goal: The main goal of this core is to provide state of the art flow cytometry/sorting and human immunology capability to the members of the cancer center.
Specific Aims: 1.Evaluate samples from a variety of sources
Project Overlap or Parallel: No scientific or budgetary overlap

CA224-020 (PI: Drake)
Title: A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors
Time commitment: .12 calendar
Supporting Agency: Bristol Myers Squibb Co
Procuring Contracting/Grants Officer: Dan Fontana
Address of Funding Agency: Route 206 & Province Line Road, Princeton, NJ 08543
Performance Period: 11/12/2013-11/11/2017
Level of Funding:
Project's Goal:
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

GO29313 (PI: Drake)
Title: A Phase 1, Open-Label, Dose-Escalation Study of The Safety and Pharmacokinetics of MOXR0916 Administered Intravenously As a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors
Time commitment: .12 calendar
Supporting Agency: Genentech Corporation
Name of Procuring Contracting/Grants Officer:
Address of Funding Agency: 1 DNA Way South, San Francisco, CA 94080
Performance Period: 07/07/2014-12/08/2017
Level of Funding:
Project's Goal: The major goal of this trial is to evaluate the safety and tolerability of MOXR0916 in patients with locally advanced or metastatic tumors
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

AWARDED SINCE LAST SUBMISSION

R21AR073013 (Christiano)
Title: Immunophenotyping of Lichen Planopilaris
Effort: 0.6 calendar months (5% effort)
Supporting Agency: NIH/NIAMS
Name of Procuring Contracting/Grants Officer: Melinda B. Nelson
Address of Funding Agency: Democracy I Building, Room 838, Bethesda, MD 20892
Performance Period: 09/01/17-8/31/19
Level of Funding:
Project's Goal: This Ancillary Studies project affords us the unique opportunity to conduct these critical immunophenotyping studies in LPP, which may have broader clinical relevance to other inflammatory and autoimmune diseases of the skin and hair follicle.
Specific Aims: Working through the CU-IMSR, Dr. Drake will assist in the design, execution and interpretation of the immunological studies in this R21 proposal. Specifically, he will assist in the interpretation of the IHC / IF studies in Aim 1, will oversee the flow and sorting experiments in Aim 2, will coordinate the serum cytokine studies in Aim 3, and will provide scientific input regarding their immunological relevance. Dr. Drake will

further assist in the preparation and editing of resultant manuscripts and will be available for consultation as needed throughout the funding period.
Role: Co-Investigator
Overlap: None

P30CA013696 (Abate-Shen)
Title: Cancer Center Support Grant
Effort: 1.2 calendar months (10% effort)
Supporting Agency: NIH/NCI
Name of Procuring Contracting/Grants Officer: Percilla L. Belin
Email of Funding Agency: belinpl@mail.nih.gov
Performance Period: 7/1/17-6/30/19
Level of Funding:
Project's Goal: The major goal of this project is to provide the organizational infrastructure and the resources to promote interdisciplinary laboratory, clinical and population based cancer research
Specific Aims: N/A
Role: Assoc. Director Clin. Res, Leader Prostate Cancer Program.
Overlap: None

COMPLETED SINCE LAST SUBMISSION

R01CA154555 (PI: Drake)
Title: Role of Tc17 cells in tumor immunotherapy
Time commitment: 2.28 calendar
Supporting Agency: National Cancer Institute
Procuring Contracting/Grants Officer: Connie Murphy
Address of Funding Agency: 6120 Executive Blvd, EPS/Suite 243, Rockville, Md. 20892-7150
Performance Period: 03/01/12- 02/28/2017
Level of Funding:
Project's Goal: These studies have broad clinical and immunological significance: successful completion of this work could transform adoptive T cell transfer for the treatment of cancer patients, and shed novel insight into fundamental aspects of CD8 function and differentiation.
Specific Aims: 1. Define the cytokine and cellular requirements for Tc17 mediated immunotherapy in vivo **2.** Understand the TCR/peptide and peptide/MHC interactions critical for Tc17 skewing in vitro. **3.** Establish the requirements for Tc17 conversion to an IFN-γ secreting phenotype 4. Determine the molecular mechanisms underlying Tc17 persistence in vivo.
Project Overlap or Parallel: No scientific or budgetary overlap

90054364(Pardoll)
Title: International Immuno-Oncology Network-IION Resource Model
Effort: .12 calendar months (1% effort)
Supporting Agency: Bristol-Myers Squibb Co
Name of Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 & Province Line Road, Princeton, NJ 08543
Performance Period: 05/07/2013-10/15/2017
Level of Funding:
Project's Goal: The major goal of this clinical research network is to conduct immunotherapy trials with novel agents including anti-KIR, anti-CD137 and others, and to collaboratively evaluate pharmacodynamics and potential biomarkers of response.
Specific Aims: 1.) Analyze immune-inhibitory networks in resected tumors employing 3 techniques for geographic localization: (i) IHC, (ii) amplified ISH, and (iii) qRT-PCR analysis of laser capture micro-dissected

(LCM) regions of leukocytic infiltration. 2. Complementary to the studies in 1, we will sort myeloid, lymphoid and cancer cells from freshly dissociated tumors in cases where enough tumor is available, allowing analysis by flow cytometry and mRNA profiling of cellular subsets for co-expression of inhibitory ligands, receptors and druggable metabolic enzymes.
Role: Co-Investigator
Overlap: None

W81XWH-15-1-0667 (Ivkov)
Title: Immune-Stimulating Combinatorial Therapy for Prostate Cancer
Effort: 0.6 calendar months (5% effort)
Supporting Agency: Department of Defense CDMRP
Name of Procuring Contracting/Grants Officer: Kathy E. Robinson
Address of Funding Agency: US Army Medical Research & Materiel Command, 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 11/1/2016 – 09/29/2017
Level of Funding:
Project's Goal: The goals of this project are to 1) induce tumor immunologic effects with focal tumor heating from magnetic iron oxide nanoparticles (MIONs) and radiation; and, 2) assess role of cytokines (e.g. ILs) and key immune cell (e.g. CD4+, CD8+ T-cell) populations in tumors to assess immune response(s) to HT and HT+RT +/- IT.
Specific Aims: 1) Assess the effects and mechanisms of HT (single treatment) on development of immunologic responses. 2) Determine effects of HT+RT +/- IT on immunologic responses.
Role: Co-Investigator
Overlap: None

90064474(Tran)
Title: Altering the natural history of metastics prostate cancer using stereotactic ablative radiotherapy and immune stimulation
Effort: .24 calendar months (2% effort)
Supporting Agency: Prostate Cancer Foundation
Name of Procuring Contracting/Grants Officer: Audrey Gardner
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401
Performance Period: 07/31/2015-10/15/2016
Level of Funding:
Project's Goal: The major goal of this project is to test the importance of treating all sites of disease with SABR in combination with the immune stimulatory agent ADXS-PSA in men with oligometastatic PCa to leverage this concept to full advantage for men suffering from metastatic PCa.
Specific Aims: 1.) To examine circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and T-cell receptor (TCR) repertoire profiling as biomarkers for men with oligometastatic prostate cancer treated with stereotactic ablative radiation therapy (SABR) alone. 2) To conduct a first-in-man trial of stereotactic ablative radiation therapy. (SABR) in combination with the immune stimulatory agent ADXS-PSA for men with oligometastatic hormone sensitive prostate cancer (HSPC).
Role: Co-Investigator
Overlap: None

90065447(Drake)
Title: The Effects of Nivolumab on the T Cell Phenotype and Tumor Microenvironment in Patients with Resectable RCC
Effort: .12 calendar months (1% effort)
Supporting Agency: Bristol Myers Squibb Co
Grants Officer: Rahbar H Tayyabkhan

Address of Funding Agency : Route 206 & Province Lane Road, Princeton, NJ 08543
Performance Period: 09/24/2015-10/15/2016
Level of Funding:
Project's Goal: The primary endpoint of this study will be safety / feasibility, given that all patients will undergo a pre-enrollment biopsy and subsequent surgical resection, we will have the ability to perform comprehensive biomarker studies using both treated and untreated tissues.
Specific Aims: 1) Quantify the effects of nivolumab monotherapy on RCC TIL in humans. 2)Understand the effects of nivolumab monotherapy on the stromal / myeloid components of the TME 3) Correlate baseline cytokine profiles (and changes in cytokine profile) with nivolumab-driven CD8 infiltration.
4) Test whether TCR clonality in the PBL of tumor correlates with induced CD8 infiltration.
Role: PI
Overlap: None

(PI:Drake)
Title: Understanding PD1 Function in RCC by Analyzing Extremes of Response - A Biomarker Study
Time commitment: .30 calendar months (2.5% effort)
Supporting agency: Bristol Myers Squibb Co
Procuring Contracting/Grants Officer: Monique R. Adams, PhD
Address of Grants Officer: Route 206 & Province Line Road, Princeton, NJ 08543
Performance period: 03/29/2016-10/15/2016
Level of funding:
Project's Goal(s): The goal of this project is to analyze a bioinformatic study of pre-existing data from RCC patients, according to according to response group (extreme responders versus extreme progressors) will yield predictive and/or on-study biomarkers and will further identify key features of response leading to the initiation of next-generation clinical trials
Specific Aims: 1. Cytokine analysis: test the hypothesis that either pre-treatment cytokine levels, or on-treatment changes in cytokine levels will correlate with response group. **2.** Microarray analysis test the hypothesis that the baseline transcriptional signature from tumor biopsies will correlate with response group. We will also test the alternative hypothesis that on-treatment changes in transcripts correlate with response group **3.** Microarray analysis: We will test the hypothesis that the baseline transcriptional signature from tumor biopsies will correlate with response group. We will also test the alternative hypothesis that on-treatment changes in transcripts correlate with response group.
Role: PI
Project Overlap or Parallel: No scientific or budgetary overlap.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

Nothing to Report

9. APPENDICES

None